Gynecologic Oncology Reports 42 (2022) 101030

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Case report

Massive hypertriglyceridemia associated with paclitaxel; a case report

Anojian Koneshamoorthy [a,*], Danielle Hulse [a], Chia Yuen Chong [b], Balasubramanian Krishnamurthy [a,c], Sumitra Ananda [b,d,e,f], Peter S. Hamblin [a,f]

[a] Department of Endocrinology and Diabetes, Western Health, Melbourne, Australia
[b] Department of Medical Oncology, Western Health, Melbourne, Australia
[c] St Vincent's Institute of Medical Research, Melbourne, Victoria, Australia
[d] Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia
[e] Epworth Freemasons, East Melbourne, Australia
[f] Department of Medicine, Western Health, University of Melbourne, St Albans, Victoria, Australia

ARTICLE INFO

Keywords:
Paclitaxel
Hypertriglyceridemia
Fallopian tube carcinoma

ABSTRACT

This report describes a patient who developed massive hypertriglyceridemia (12,488 mg/dL or 141 mmol/L) during paclitaxel and carboplatin adjuvant chemotherapy for high grade serous fallopian tube carcinoma. Paclitaxel was thought to be the causative agent and she had normal triglyceride levels following a change to carboplatin and gemcitabine. To our knowledge, this is the highest reported triglyceride level associated with paclitaxel. Measurement of serum lipids should be considered in individuals receiving taxane chemotherapy, especially in those with type 2 diabetes mellitus or a history of dyslipidemia.

1. Introduction

Fallopian tube serous carcinomas are malignancies originating from the transformation of the salpingeal mucosa (Stasenko et al., 2019). The incidence is reported to be 0.36 to 0.41 per 100,000 women per year with a median age of 64 years (Stewart et al., 2007).

Given the similarities in clinical behaviour with ovarian, fallopian tube and peritoneal carcinomas, the treatment approach is the same (Stasenko et al., 2019). When optimal cytoreduction can be achieved, surgical debulking is recommended for stage III or IV disease, followed by adjuvant chemotherapy which is traditionally a platinum doublet of carboplatin and paclitaxel (Stasenko et al., 2019).

Hypertriglyceridemia is a common form of dyslipidemia (Brunzell, 2007). Several genetic disorders can cause hypertriglyceridemia including familial combined hyperlipidemia, residual dyslipidemia in persons with well controlled type 2 diabetes mellitus and familial hypoalphalipoproteinemia (Brunzell, 2007). Uncontrolled diabetes, alcohol consumption and treatment with several drugs can lead to secondary hypertriglyceridemia (Brunzell, 2007). Here we report a case of massive hypertriglyceridemia attributed to paclitaxel, utilised to treat high grade fallopian tube serous carcinoma.

2. Case presentation

A 71-year-old woman was diagnosed with a stage III high grade serous fallopian tube carcinoma with omental disease in September 2021, following a diagnostic laparoscopy with salpingectomy and omental biopsy. Immunostains where positive for p53, WT1, PAX 8, p16, CK7, ER (95%) and negative for calretinin and CK20. Her CA125 at diagnosis was 101 U/mL (0–35). She had a history of well controlled mixed dyslipidemia, and insulin-dependent type 2 diabetes for more than 20 years, (HbA1c was 7.1 % (54 mmol/mol) 13 days before the first chemotherapy cycle, indicating good diabetes control and historical HbA1c of 7.2% (55 mmol/mol) dating back to 2017).

She also had hypertension, untreated mild subclinical hypothyroidism, gastro-esophageal reflux disease, osteoporosis, depression and a past history of T8/T9 vertebral tuberculosis in 2017. Her medications were rosuvastatin 10 mg daily, telmisartan 40 mg daily, amlodipine 10 mg daily, escitalopram 20 mg daily, Ryzodeg® insulin (degludec/insulin aspart) twice daily, linagliptin 5 mg daily, metformin 1000 mg daily, alendronate 70 mg weekly and nizatidine 150 mg daily.

She received the first of three cycles of paclitaxel in cremophor EL (CrEL) excipient on 29th September 2021 at a dose of 313 mg (175 mg/m2) and carboplatin AUC 6 (691 mg). After the three cycles, the plan was for her to be assessed for suitability of surgical debulking, followed

* Corresponding author.
E-mail address: anojian.koneshamoorthy@svha.org.au (A. Koneshamoorthy).

https://doi.org/10.1016/j.gore.2022.101030
Received 29 April 2022; Received in revised form 4 June 2022; Accepted 6 June 2022

by a further three cycles of adjuvant chemotherapy. Dexamethasone was administered in a dose of 12 mg intravenously on the day of chemotherapy, followed by 4 mg orally twice daily for the first two days following chemotherapy. She experienced grade 1 painful peripheral neuropathy following the first cycle, for which she was prescribed gabapentin 300 mg daily.

Seventeen days after her third cycle of chemotherapy, she was incidentally found to have massive hypertriglyceridemia with triglyceride level of 12,488 mg/dL (141 mmol/L) and total cholesterol level of 1369 mg/dL (35.4 mmol/L) on blood testing arranged for a routine diabetes clinic appointment. The laboratory urgently contacted the endocrinologist who had requested the blood test. The patient was then contacted and reported that she felt well. She had no symptoms to suggest acute pancreatitis.

There was no prior history of severe hyperlipidemia. She was commenced on rosuvastatin 10 mg in 2017 with total cholesterol of 232 mg/dL (6.0 mmol/L) and triglycerides of 124 mg/dL (1.4 mmol/L). Prior testing in 2010 demonstrated a normal lipid panel with total cholesterol of 135 mg/dL (3.5 mmol/L) and 44 mg/dL (0.5 mmol/L). She had no clinical signs of acanthosis nigricans or eruptive xanthomas. Her most recent total cholesterol level prior to chemotherapy was 155 mg/dL (4.0 mmol/L) and triglyceride was 177 mg/dL (2.0 mmol/L), 13 days before her first cycle. Other investigations at the time of the severe hypertriglyceridemia demonstrated deterioration of her diabetes control with HbA1c of 8.9% (74 mmol/mol), with cyclical use of dexamethasone, and mild subclinical hypothyroidism with an elevated thyroid stimulating hormone (TSH) of 6.13 mIU/L (0.5–4.0) but normal free thyroxine (FT4) of 1.16 ng/dL or 14.9 pmol/L (0.78–1.79 ng/dL or 10–23 pmol/L). These thyroid function tests were similar to previous levels in May 2021 (TSH 5.26 mIU/L, FT4 of 1.1 ng/dL or 13.7 pmol/L).

The incidental discovery of massive hypertriglyceridemia raised concerns for the potential development of severe pancreatitis. Serum lipase was measured urgently and fortunately was found to be only minimally elevated at 61 U/L (0–60). It was noted in retrospect that on previous blood tests taken between February and September 2021 she had mildly elevated lipase levels between 94 and 106 U/L, however had no history of abdominal pain to suggest pancreatitis. Alkaline phosphatase was 109 U/L (30–110), gamma-glutamyl transferase was 71 U/L (0–35), alanine aminotransferase was 19 U/L (0–35) and bilirubin was 0.35 mg/dL (6 micromol/L) (<1.17 mg/dL).

In light of the risk for severe necrotizing pancreatitis, she was admitted to hospital for urgent triglyceride lowering management. This consisted of fasting, intravenous insulin and glucose infusions, fenofibrate 145 mg daily and fish oil 9 g/day equating to 2700 mg omega-3. Additionally, the rosuvastatin dose was increased from 10 mg daily to 40 mg daily. Thyroxine was also commenced at an initial dose of 25 micrograms daily to treat her mild subclinical hypothyroidism. Fasting and the insulin/dextrose infusion continued for four days. The triglyceride level progressively fell, and she was discharged from hospital after seven days, at which time the triglyceride concentration was 2188 mg/dL (24.7 mmol/L) and total cholesterol was 704 mg/dL (18.2 mmol/L). By one week after discharge, the triglycerides were down to 354 mg/dL (4.0 mmol/L) and by 12 days after discharge, they were normal at 159 mg/dL (1.8 mmol/L) and total cholesterol was 217 mg/dL (5.6 mmol/L). The lipase peaked at 136 U/L on Day 5 of the admission and fell to normal by Day 8 (58 U/L).

The time course of the serum triglyceride concentration changes is demonstrated in Fig. 1.

After reviewing the literature, paclitaxel was thought to be the likely cause of the hypertriglyceridemia, so she was changed to a taxane-free chemotherapy regimen of carboplatin and gemcitabine for subsequent cycles. Following the change to gemcitabine, her triglyceride levels have remained normal (Fig. 1). Fish oil was ceased after 6 weeks but she remains on fenofibrate, and her triglyceride level was normal at 106 mg/dL (1.2 mmol/L). It had been planned for her to have debulking surgery around the time she developed hypertriglyceridemia; however, this was postponed in light of the heightened perioperative risk with severe hypertriglyceridemia. Her CA125 level had reduced to 34 U/mL in January 2022 and follow up computed tomography demonstrated persistent omental nodularity, with minimal decrease in volume. She has since undergone optimal debulking surgery, and will be commencing PARP inhibitor, Niraparib, as maintenance therapy.

3. Discussion

Platinum doublet chemotherapy is considered first line adjuvant chemotherapy for fallopian tube serous carcinomas (Stasenko et al., 2019). Paclitaxel in combination with cisplatin or carboplatin has been occasionally linked with hypertriglyceridemia, however the mechanism of this adverse event is not fully understood (Lander et al., 2020; Watanabe et al., 2015; Wang et al., 2017 Feb 1). Lander et al described a patient who developed severe hypertriglyceridemia (1871 mg/dL) after the 4th cycle of intraperitoneal cisplatin and paclitaxel to treat stage IIIC fallopian tube serous carcinoma. Intraperitoneal administration of cisplatin and paclitaxel has an increased frequency of adverse events compared with intravenous, including metabolic events (Armstrong et al., 2006).

Watanabe et al reported 11 of 17 individuals in a prospective study who received paclitaxel and carboplatin developed hypertriglyceridemia at 2.8 ± 0.6 courses (Watanabe et al., 2015). Triglyceride levels in these 11 individuals increased from 119 ± 23.3 to 271.5 ± 108.7 mg/dL (Watanabe et al., 2015). Patients with diabetes were excluded from that study. Wang et al reported temporally associated hypertriglyceridemia in three women with each cycle of carboplatin and

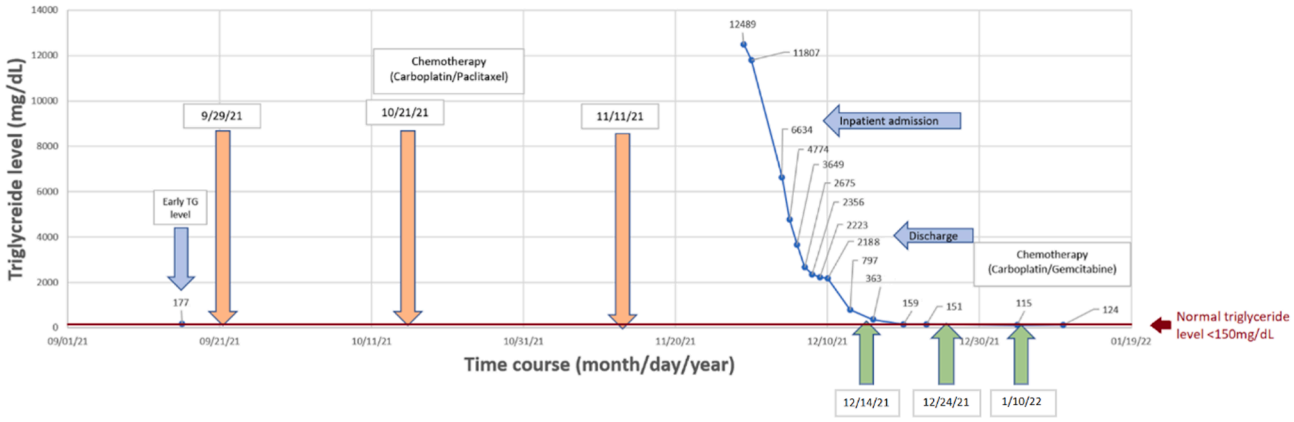

Fig. 1. Time course of serum triglyceride concentrations. Orange arrows represent each cycle of carboplatin/paclitaxel chemotherapy. Green arrows represent each cycle of carboplatin/gemcitabine. Red line represents normal upper limit of serum triglyceride concentration of 150 mg/dL (1.7 mmol/L).

paclitaxel (Wang et al., 2017 Feb 1). The highest recorded triglyceride level was however<5 mmol/L (<443 mg/dL) (Wang et al., 2017).

Saito et al recently described a case of hypertriglyceridemia attributed to docetaxel, another taxane-containing chemotherapy agent, used to treat stage IIB breast cancer. The highest recorded triglyceride level was 770 mg/dL (19.9 mmol/L) in that case (Saito et al., 2021).

Dai et al have reported that paclitaxel induces aerobic glycolysis and hypertriglyceridemia (Dai et al., 2021). These metabolic effects are proposed to be linked with the excipient CrEL, which is unique to paclitaxel as compared with other taxane-containing chemotherapies. Paclitaxel, which is hydrophobic, is formulated with CrEL, which enhances drug solubility (Scripture et al., 2005). Dai et al demonstrated patients with breast cancer developed higher triglyceride levels in the group that received paclitaxel with CrEL, compared to abraxane (nanoparticle albumin-bound paclitaxel), docetaxel and non-taxanes (Dai et al., 2021). There was a triglyceride increase in all four groups, however in the paclitaxel with CrEL group, 8% developed triglyceride concentrations above 131 mg/dL (3.4 mmol/L) and 44% demonstrated a 70% rise in triglycerides after this therapy. CrEL was found to upregulate angiopoietin like 4, which is a major determinant of triglyceride levels (Aryal et al., 2019) and pre-medication with dexamethasone further accentuates this effect (Scripture et al., 2005).

The risk of acute pancreatitis increases with the concentration of serum triglyceride. The risk is approximately 5% for triglycerides > 1000 mg/dL (11.3 mmol/L), and 10–20% for triglycerides > 2000 mg/dL (22.6 mmol/L) (Scherer et al., 2014). Our case had serum triglyceride concentrations more than seventy times the upper limit of normal, which potentially put her at a high risk of life-threatening necrotizing pancreatitis.

This case would have escaped attention if she had not been scheduled to have routine diabetes clinic blood tests. The incidence of hypertriglyceridemia related to taxane based chemotherapy is unclear, given that lipids are not routinely assessed. At our institution, routine full blood count, renal function test and liver function test are monitored prior to each cycle of chemotherapy, in addition to hepatitis B serology screening prior to commencement. Lipid levels are not part of our standard practice for monitoring.

Our patient had several factors which may have pre-disposed her to massive hypertriglyceridemia: a history of dyslipidemia, type 2 diabetes, post-menopausal status, glucocorticoid therapy, and subclinical hypothyroidism. While these factors may have predisposed her to hypertriglyceridemia, the use of paclitaxel was clearly temporally linked, and in addition, hypertriglyceridemia has not recurred when using alternative chemotherapy agents. All of this suggests the paclitaxel was responsible. It is possible that she has a genetic defect pre-disposing her to this reaction. Genetic studies have not been performed.

We suggest it is important to assess lipid panels prior to and serially in patient receiving taxane chemotherapy. This is especially relevant to patients with a history of type 2 diabetes or dyslipidemia.

In summary, we report a case of severe hypertriglyceridemia attributed to paclitaxel use. To our knowledge this is the most severe triglyceride elevation reported related to paclitaxel. Treating oncologists should be aware of this potential effect and monitoring of lipid panels should be considered in individuals receiving this chemotherapy regimen, especially in people with type 2 diabetes or a history of dyslipidemia. This would minimise harmful potential sequelae of hypertriglyceridemia and enable prompt commencement of triglyceride lowering therapy and/or alteration of administered chemotherapy.

Consent

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Funding

No funding or grant support.

CRediT authorship contribution statement

Anojian Koneshamoorthy: Writing – original draft, Investigation, Visualization. **Danielle Hulse:** Investigation, Visualization. **Chia Yuen Chong:** Writing – review & editing. **Balasubramanian Krishnamurthy:** Writing – review & editing. **Sumitra Ananda:** Writing – review & editing. **Peter S. Hamblin:** Investigation, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Stasenko, M., Fillipova, O., Tew, W.P., 2019. Fallopian tube carcinoma. J. Oncol. Pract. 15 (7), 375–382.
Stewart, S.L., Wike, J.M., Foster, S.L., Michaud, F., 2007. The incidence of primary fallopian tube cancer in the United States. Gynecol. Oncol. 107 (3), 392–397.
Brunzell, J.D., 2007. Hypertriglyceridemia. N. Engl. J. Med. 357 (10), 1009–1017.
Lander, M., Abedin, Y., Gabrilovich, S., Marcus, J.Z., 2020. Severe hypertriglyceridemia during treatment with intraperitoneal cisplatin and paclitaxel for advanced stage fallopian tube carcinoma. Gynecol. Oncol. Rep. 32, 100552. https://doi.org/10.1016/j.gore.2020.100552.
Watanabe, A., Tanabe, A., Maruoka, R., Nakamura, K., Hatta, K., Ono, Y.J., Terai, Y., Ohmichi, M., 2015. Fibrates protect against vascular endothelial dysfunction induced by paclitaxel and carboplatin chemotherapy for cancer patients: a pilot study. Int. J. Clin. Oncol. 20 (4), 829–838.
Wang, G., Su, C., Yin, T., 2017. Paclitaxel and platinum-based chemotherapy results in transient dyslipidemia in cancer patients. Mol. Clin. Oncol. 6 (2), 261–265.
Armstrong, D.K., Bundy, B., Wenzel, L., Huang, H.Q., Baergen, R., Lele, S., Copeland, L. J., Walker, J.L., Burger, R.A., 2006. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N. Engl. J. Med. 354 (1), 34–43.
Saito, Y., Takekuma, Y., Takeshita, T., Sugawara, M., 2021. Severe hypertriglyceridemia induced by docetaxel: a novel case report. Case Rep. Oncol. 14 (3), 1277–1282.
Dai, Q., Liu, X., He, T., Yang, C., Jiang, J., Fang, Y., Fu, Z., Yuan, Y., Bai, S., Qiu, T., Yin, R., Ding, P., Chen, J., Li, Q., 2021. Excipient of paclitaxel induces metabolic dysregulation and unfolded protein response. Iscience 24 (10), 103170. https://doi.org/10.1016/j.isci.2021.103170.
Scripture, C.D., Figg, W.D., Sparreboom, A., 2005. Paclitaxel chemotherapy: from empiricism to a mechanism-based formulation strategy. Ther. Clin. Risk Manag. 1 (2), 107–114.
Aryal, B., Price, N.L., Suarez, Y., Fernández-Hernando, C., 2019. ANGPTL4 in metabolic and cardiovascular disease. Trends Mol. Med. 25 (8), 723–734.
Scherer, J., Singh, V., Pitchumoni, C.S., Yadav, D., 2014. Issues in hypertriglyceridemic pancreatitis-an update. J. Clin. Gastroenterol. 48 (3), 195.